

PRELIMINARY AMENDMENT
Attorney Docket No. Q86357

AMENDMENTS TO THE SPECIFICATION

Please replace paragraph no. 3, page 15, with the following amended paragraph:

Figure 4 is the ^1H -NMR spectrum (DMSO-d₆, TMS) of the Anhydrous aAripiprazole anhydride eCrystals B obtained in Example 1.

Please replace paragraph no. 4, page 15, with the following amended paragraph:

Figure 5 is the powder X-ray diffraction diagram of the Anhydrous aAripiprazole anhydride eCrystals B obtained in Example 1.

Please replace paragraph no. 1, page 19, with the following amended paragraph:

Aripiprazole and aripiprazole metabolites to be used in the present invention may be any of form, for example, free bases, polymorphisms of every type of crystal, hydrate, salts (acid addition salts, etc.) and the like. Among of these forms, Anhydrous aAripiprazole anhydride eCrystals B is a preferred form.

Please replace paragraph no. 2, page 19, with the following amended paragraph:

As to method for preparing the Anhydrous aAripiprazole anhydride eCrystals B, for example it is prepared by heating aripiprazole hydrate A as follows.

Please replace the heading of paragraph no. 3 and paragraph no. 3, page 21, with the following amended heading and paragraph:

Anhydrous Aripiprazole Anhydride Crystals B

"Anhydrous Aripiprazole anhydride eCrystals B" of the present invention have the physicochemical properties given in (6)-(10) below.

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Please replace the heading of paragraph no. 2 and paragraph no. 2, which bridges pages 22 and 23, with the following amended heading and paragraph:

Method for preparing Anhydrous Aripiprazole Anhydride Crystals B

The Anhydrous aAripiprazole anhydride eCrystals B of the present invention are prepared for example by heating the aforementioned aripiprazole hydrate A at 90-125°C. The heating time is generally about 3-50 hours, but cannot be stated unconditionally, because it differs depending on heating temperature. The heating time and heating temperature are inversely related, so that for example when the heating time is longer, then the heating temperature is lower, and when the heating temperature is higher then the heating time is shorter. Specifically, if the heating temperature of aripiprazole hydrate A is 100°C, the heating time may be 18 hours or more, or preferably about 24 hours. If the heating temperature of aripiprazole hydrate A is 120°C, on the other hand, the heating time may be about 3 hours. The Anhydrous aAripiprazole anhydride eCrystals B of the present invention can be prepared with certainty by heating aripiprazole hydrate A for about 18 hours at 100°C, and then heating it for about 3 hours at 120°C. The Anhydrous aAripiprazole anhydride eCrystals B of the present invention can also be obtained if the heating time is extended still further, but this method may not be economical.

Please replace paragraph no. 1, page 23, with the following amended paragraph:

When small particle size is not required for the formulation, e.g., when drug substance is being prepared for injectable or oral solution formulations, Anhydrous aAripiprazole anhydride eCrystals B can be also obtained by the following process.

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Please replace paragraph no. 2, bridging pages 23 and 24, with the following amended paragraph:

Anhydrous Aripiprazole anhydride eCrystals B of the present invention are prepared for example by heating conventional anhydrous aripiprazole anhydride crystals at 90-125°C. The heating time is generally about 3-50 hours, but cannot be stated unconditionally because it differs depending on heating temperature. The heating time and heating temperature are inversely related, so that for example if the heating time is longer, the heating temperature is lower, and if the heating time is shorter, the heating temperature is higher. Specifically, if the heating temperature of the anhydrous aripiprazole anhydride crystals is 100°C, the heating time may be about 4 hours, and if the heating temperature is 120°C the heating time may be about 3 hours.

Please replace paragraph no. 1, page 24, with the following amended paragraph:

Furthermore, Anhydrous aAripiprazole anhydride eCrystals B of the present invention are prepared for example, by heating conventional aripiprazole hydrate at 90-125°C. The heating time is generally about 3-50 hours, but cannot be stated unconditionally because it differs depending on heating temperature. The heating time and heating temperature are inversely related, so that for example, if the heating time is longer, the heating temperature is lower, and if the heating time is shorter, the heating temperature is higher. Specifically, if the heating temperature of the aripiprazole hydrate is 100°C, the heating time may be about 24 hours, and if the heating temperature is 120°C the heating time may be about 3 hours.

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Please replace paragraph no. 2, page 24, with the following amended paragraph:

The anhydrous aripiprazole ~~anhydride~~ crystals which are the raw material for preparing the Anhydrous aAripiprazole anhydride eCrystals B of the present invention are prepared for example by Method a or b below.

Please replace paragraph no. 3, which bridges pages 24 and 25, with the following amended paragraph:

Conventional anhydrous aripiprazole ~~anhydride~~ crystals are prepared by well-known methods, as described in Example 1 of Japanese Unexamined Patent Publication No. 191256/1990.

Please replace the heading of paragraph nos. 2 and 3, page 25, with the following amended heading:

"Method b": Process for preparing conventional Anhydrous Aripiprazole Anhydride

Please replace paragraph no. 3, page 25, with the following amended paragraph:

The aripiprazole hydrate which is the raw material for preparing the Anhydrous aAripiprazole anhydride eCrystals B of the present invention is prepared for example by Method c below.

Please replace paragraph no. 4, page 25, with the following amended paragraph:

Aripiprazole hydrate is easily obtained by dissolving the anhydrous aripiprazole ~~anhydride~~ crystals obtained by Method a above in a hydrous solvent, and heating and then cooling the resulting solution. Using this method, aripiprazole hydrate is precipitated as crystals in the hydrous solvent.

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Please replace paragraph no. 3, page 35, with the following amended paragraph:

Capsules are prepared according to ordinary methods by mixing carbostyryl derivatives such as anhydrous aripiprazole ~~anhydride~~ crystals as the first ingredient and serotonin reuptake inhibitor as the second ingredient, and the various carriers described above and packing them in hard gelatin capsules, soft capsules hydroxypropylmethyl cellulose capsules (HPMC capsules) and the like.

Please replace paragraph no. 1, page 41, with the following amended paragraph:

The crude product of aripiprazole (30 g) obtained above was recrystallized from 450 ml of ethanol according to the methods described in Japanese Unexamined Patent Publication No. 191256/1990, and the resulting crystals were dried at 80°C for 40 hours to obtain anhydrous aripiprazole ~~anhydride~~ crystals. The yield was 29.4 g (98.0%).

Please replace paragraph no. 2, page 41, with the following amended paragraph:

The melting point (mp) of these anhydrous aripiprazole ~~anhydride~~ crystals was 140°C, which is identical to the melting point of the anhydrous aripiprazole ~~anhydride~~ crystals described in Japanese Unexamined Patent Publication No. 191256/1990.

Please replace paragraph no. 1, page 42, with the following amended paragraph:

The wet-state aripiprazole hydrate crystals obtained above were dried at 80°C for 30 hours to obtain 6480 g (93.5%) of anhydrous aripiprazole ~~anhydride~~ crystals. The melting point (mp) of these crystals was 139.5°C.

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Please replace paragraph no. 5, which bridges pages 44 and 45, with the following amended paragraph:

The aripiprazole hydrate A (powder) (44.29 kg) obtained in the Reference Example 4 was dried at 100°C for 18 hours by using a hot air dryer and further heated at 120°C for 3 hours, to obtain 42.46 kg (yield; 99.3 %) of Anhydrous aAripiprazole anhydride eCrystals B. These Anhydrous aAripiprazole anhydride eCrystals B had a melting point (mp) of 139.7°C.

Please replace paragraph no. 1, page 45, with the following amended paragraph:

The Anhydrous aAripiprazole anhydride eCrystals B obtained above had an ¹H-NMR spectrum (DMSO-d₆, TMS) which was substantially identical to the ¹H-NMR spectrum shown in Figure 4. Specifically, they had characteristic peaks at 1.55-1.63 ppm (m, 2H), 1.68-1.78 ppm (m, 2H), 2.35-2.46 ppm (m, 4H), 2.48-2.56 ppm (m, 4H + DMSO), 2.78 ppm (t, J = 7.4 Hz, 2H), 2.97 ppm (brt, J = 4.6 Hz, 4H), 3.92 ppm (t, J = 6.3 Hz, 2H), 6.43 ppm (d, J = 2.4 Hz, 1H), 6.49 ppm (dd, J = 8.4 Hz, J = 2.4 Hz, 1H), 7.04 ppm (d, J = 8.1 Hz, 1H), 7.11-7.17 ppm (m, 1H), 7.28-7.32 ppm (m, 2H) and 10.00 ppm (s, 1H).

Please replace paragraph no. 2, page 45, with the following amended paragraph:

The Anhydrous aAripiprazole anhydride eCrystals B obtained above had a powder x-ray diffraction spectrum which was substantially the identical to the powder x-ray diffraction spectrum shown in Figure 5. Specifically, they had characteristic peaks at 2θ = 11.0°, 16.6°, 19.3°, 20.3° and 22.1°.

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Please replace paragraph no. 3, page 45, with the following amended paragraph:

The Anhydrous aAripiprazole anhydride eCrystals B obtained above had remarkable infrared absorption bands at 2945, 2812, 1678, 1627, 1448, 1377, 1173, 960 and 779 cm⁻¹ on the IR (KBr) spectrum.

Please replace paragraph no. 4, which bridges pages 45 and 46, with the following amended paragraph:

The Anhydrous aAripiprazole anhydride eCrystals B obtained above exhibited an endothermic peak near about at 141.5°C in thermogravimetric/differential thermal analysis. The Anhydrous aAripiprazole anhydride eCrystals B obtained above exhibited an endothermic peak near about at 140.7°C in differential scanning calorimetry.

Please replace Formulation Sample Example 1, page 53, with the following amended one:

Formulation Sample Example 1

<u>Anhydrous Aripiprazole Anhydride Crystals B</u>	5 mg
Fluoxetine	20 mg
Starch	131 mg
Magnesium stearate	4 mg
<u>Lactose</u>	<u>60 mg</u>
Total	220 mg

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Please replace Formulation Sample Example 2, page 54, with the following amended

one:

Formulation Sample Example 2

Anhydrous Aripiprazole Anhydride Crystals B	5 mg
Duloxetine	20 mg
Starch	131 mg
Magnesium stearate	4 mg
<u>Lactose</u>	<u>60 mg</u>
Total	220 mg

Please replace Formulation Sample Example 3, page 54, with the following amended

one:

Formulation Sample Example 3

Anhydrous Aripiprazole Anhydride Crystals B	5 mg
Venlafaxine	75 mg
Starch	131 mg
Magnesium stearate	4 mg
<u>Lactose</u>	<u>60 mg</u>
Total	275 mg

Please replace Formulation Sample Example 4, page 55, with the following amended

one:

Formulation Sample Example 4

Anhydrous Aripiprazole Anhydride Crystals B	5 mg
Milnacipran	50 mg
Starch	131 mg
Magnesium stearate	4 mg
<u>Lactose</u>	<u>60 mg</u>
Total	250 mg

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Please replace Formulation Sample Example 5, page 55, with the following amended one:

Formulation Sample Example 5

Anhydrous Aripiprazole Anhydride Crystals B	5 mg
Citalopram	20 mg
Starch	131 mg
Magnesium stearate	4 mg
<u>Lactose</u>	<u>60 mg</u>
Total	220 mg

Please replace Formulation Sample Example 6, page 56, with the following amended one:

Formulation Sample Example 6

Anhydrous Aripiprazole Anhydride Crystals B	5 mg
Fluvoxamine	50 mg
Starch	131 mg
Magnesium stearate	4 mg
<u>Lactose</u>	<u>60 mg</u>
Total	250 mg

Please replace Formulation Sample Example 7, page 56, with the following amended one:

Formulation Sample Example 7

Anhydrous Aripiprazole Anhydride Crystals B	5 mg
Paroxetine	20 mg
Starch	131 mg
Magnesium stearate	4 mg
<u>Lactose</u>	<u>60 mg</u>
Total	220 mg

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Please replace Formulation Sample Example 8, page 57, with the following amended

one:

Formulation Sample Example 8

Anhydrous Aripiprazole Anhydride Crystals B	5 mg
Sertraline	50 mg
Starch	131 mg
Magnesium stearate	4 mg
<u>Lactose</u>	<u>60 mg</u>
Total	250 mg

Please replace Formulation Sample Example 9, page 57, with the following amended

one:

Formulation Sample Example 9

Anhydrous Aripiprazole Anhydride Crystals B	5 mg
Escitalopram	10 mg
Starch	131 mg
Magnesium stearate	4 mg
<u>Lactose</u>	<u>60 mg</u>
Total	210 mg